NATIONAL HEMOPHILIA FOUNDATION
for all bleeding disorders

July 1, 2022

VIA ELECTRONIC SUBMISSION

Division of Dockets Management
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

CITIZEN PETITION

Dear Sir or Madam,

The National Hemophilia Foundation (NHF) respectfully submits this Citizen Petition pursuant to 21 U.S.C. §§ 10.25 and 10.30 to request that if it approves the products, the U.S. Food and Drug Administration (FDA) require a Risk Evaluation and Mitigation Strategy (REMS) as a condition of approval for both valoctocogene roxaparvovec, a BioMarin investigational gene therapy under regulatory review for the treatment of severe hemophilia A, and etranacogene dezaparvovec, a CSL Behring investigational gene therapy currently under review for the treatment of hemophilia B. NHF is the nation's leading advocacy organization working to ensure that individuals affected by hemophilia and related inherited blood disorders have timely access to high quality medical care and services and safe and effective products to treat their disease, regardless of financial circumstances or place of residence.

About Hemophilia

Hemophilia is a rare, chronic blood disorder affecting approximately 35,000 males in the US. There are also similar inherited bleeding disorders, such as von Willebrand disease (VWD), that affect an estimated three million Americans, the majority of whom remain undiagnosed and without care, leading to excessive healthcare expenditures, morbidity, and mortality. Others are affected by rare factor deficiencies or inherited platelet disorders. Currently, hemophilia treatments involve patients infusing high-cost clotting factor therapies to replace missing or deficient blood proteins or, in the case of coagulation factor VIII deficiency, injection of a monoclonal antibody to replace the deficient clotting factor activity. It is an exciting time for the hemophilia community, with gene therapy products on the horizon.

Most people with hemophilia receive care at the national network of hemophilia treatment centers (HTCs). Since 1974, Congress has authorized and funded the hemophilia program at the Health Resources and Services Administration (HRSA). HTCs, authorized under section 501(a)(2) of the Social Security Act, deliver integrated, patient-centered care, reduce morbidity and mortality, and lower overall healthcare costs associated with this patient population. Studies have consistently demonstrated the value of the HTC network at improving patient outcomes. For example, a recent study from 2019 found that there was 47.1% lower frequency of emergency department use among patients being cared for at an HTC compared to patients cared for outside of the HTC network, and that HTC patients are 30% more likely to be treated with prophylaxis, the current standard of care.[i] In 2020, the CDC published a Mortality and Morbidity Weekly Review article with an evaluation of the history of the HTC program.[ii] There is a growing need for more specialized clinical care as spelled out in a recent publication, Integrated Hemophilia Patient Care via a National Network of Care Centers in the United States: A Model for Rare Coagulation Disorders.[iii]

Action Requested

NHF respectfully urges that the FDA:

1. **Require a REMS as a condition of approving valoctocogene roxaparvovec and etranacogene dezaparvovec.**
2. **Include the eligibility (inclusion and exclusion) criteria utilized in the clinical trials on the drug label.**

Statement of Grounds

FDA should require a REMS as a condition of approving valoctocogene roxaparvovec and etranacogene dezaparvovec. Specifically, the REMS should include Elements to Assure Safe Use (ETASU) that include the following elements:

1. Training and education for physicians and health care providers (HCPs) on gene therapy and the management of people with hemophilia who receive a gene therapy product.
2. Training and education on shared decision making for physicians and HCPs who will evaluate, administer, and follow people with hemophilia who are candidates to receive a gene therapy product.
3. Facilities administering valoctocogene roxaparvovec and etranacogene dezaparvovec must be certified.
4. Valoctocogene roxaparvovec and etranacogene dezaparvovec are only to be administered at a federally recognized hemophilia treatment center with knowledge and expertise in evaluating, administering, and managing people with hemophilia who have received investigational gene therapy products.
5. Individuals receiving valoctocogene roxaparvovec and etranacogene dezaparvovec be enrolled in a registry in order to collect robust data, including on adverse events of interest.

The Federal Food, Drug, and Cosmetic Act authorizes FDA to require the submission of a REMS if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (21 U.S.C. § 355-1(a)). In making this determination, FDA is required to consider six factors. The discussion below lays out the six factor and how they apply to both products.

1. The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug;

Both known and unknown adverse events exist. Steroid use should be an outcome of interest, given the reported required use of glucocorticoids in the two-year data analysis for valoctocogene roxaparvovec (79.1% of participants received steroids for a median treatment duration of 230 days), and the high proportion of related adverse events.[iv] Additionally, recent events with adeno-associated virus (AAV) therapy including thromboses, requirement for prophylactic anticoagulant treatment, as well as three reports of cancer (deemed unrelated to the vector) highlight the many unknowns.[v] Lastly, NHF directs the FDA to the coreHEM core outcome set for an updated list of adverse events of interest within gene therapy. These are grouped in three domains: short-term adverse events (liver toxicity, short term immune response to FVIII/FIX, immune response to gene therapy, thrombosis), long-term adverse events (development of other disorders, vector integration into host genome, duration of vector-neutralizing response) and mortality.[vi]

2. The expected benefit of the drug with respect to the disease or condition;

The goal is for each treatment to be a one-time therapy that relieves patients from the treatment burdens of ongoing prophylaxis and/or factor VIII trough levels that place them at significant risk of bleeding when their circulating FVIII activity level drops below a therapeutic level. However, the gene therapy requires rigorous adherence to a demanding follow-up regimen, which includes significant lifestyle modifications including abstinence from alcohol ingestion and use of barrier contraception. Currently, the efficacy data demonstrates similar impacts on bleeding rates compared to factor replacement therapy in adherent individuals.

3. The seriousness of the disease or condition that is to be treated with the drug;

Hemophilia is a life-long inheritable bleeding disorder due to the deficiency of the activity of coagulation factor VIII (hemophilia A) or IX (hemophilia B). The life expectancy for people with hemophilia has dramatically improved over the past five decades due to the combination of the availability of integrated comprehensive care delivered by a network of care centers and therapeutic drug innovations. Without treatment, people with hemophilia can bleed internally, sometimes as a result of trauma, but sometimes simply from everyday activities. This bleeding can lead to severe joint damage and permanent disability, or can even lead to death, if a bleed involves major organs and/or the brain.

Individuals living with hemophilia have complex, lifelong medical needs. They depend on the ongoing use of prescription biologic medications (clotting factor or other novel therapies) to avoid and/or treat painful bleeding episodes, that if left untreated, could lead to permanent joint damage and debilitating lifelong pain, and as mentioned above, even death. These biologic medications, derived from human blood plasma or created by recombinant technology, are highly effective, but extremely expensive. Since there are no less expensive generic or biosimilar equivalents, the annual cost can exceed several hundred thousand dollars annually.

4. Whether the drug is a new molecular entity;

As set forth by FDA, a new chemical entity (NCE) is "a drug that contains no active moiety that has been approved by FDA in any other application submitted under section 505(b) of the act (21 CFR 314.108(a)). Under this definition, both valoctocogene roxaparvovec, a BioMarin investigational gene therapy under regulatory review for the treatment of severe hemophilia A, and etranacogene dezaparvovec, a CSL Behring investigational gene therapy currently under review for the treatment of hemophilia B, should both be considered a new chemical entity.

The durability of effect on factor activity levels and/or annualized bleed rates of valoctocogene roxaparvovec and etranacogene dezaparvovec is unknown. We do know, however, that AAV gene therapy can be administered only a single time. At this time, the immune response will preclude re-administration of any other currently identified AAV vectors. At present, no solution exists for this problem, meaning that if a patient gets a suboptimal response or loses activity over a comparatively short period, they have lost their opportunity for subsequent AAV gene therapy.[vii] In that respect, the duration of the effects of the treatment are lifelong.

5. The estimated size of the population likely to use the drug.

Finally, approximately 35,000 males in the U.S. have hemophilia A and B with approximately one-fifth of that number having hemophilia B. Clinical trials have imposed exclusionary criteria that reduce the eligible population – such as excluding women with hemophilia, people with mild hemophilia, people with pre-existing immunity to AAV 5, prior history of an inhibitor, and/or significant liver disease, along with other exclusion criteria. In addition, many people with hemophilia will choose not to receive gene therapy at this time. Therefore, the NHF estimates that not more than 2,000 people with hemophilia A and a fraction of those with hemophilia B will choose to receive a commercial gene therapy product.

In order to ensure the optimal outcomes for people who do wish to receive a gene therapy product, FDA should authorize/approve the products use in the same population as studied in the controlled clinical trials precluding off-label use.

Environmental impact

Petitioner claims a categorical exclusion under 21 C.F.R. § 25.31.

Economic Impact

Petitioner will submit information on the economic impact if requested by the FDA.

The undersigned certifies, that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petition which are unfavorable to the petition.

Thank you for your consideration.

Sincerely,

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